REMARKS

Claims 16-22 and 54-63 are pending. Claim 16 is amended herewith. Claims 73-76 are added herewith. Claims 54-63 are withdrawn from consideration as being drawn to a nonelected invention. Thus, claims 16-22 and 73-76 are under examination. Support for the new and amended claims appears throughout the application and claims as originally filed, including at p. 26, line 9 to p. 28, line 6, and the paragraph bridging pages 30-31. No new matter is added by these amendments. Applicants make such amendments without prejudice to pursuing the originally presented or canceled subject matter in a later application claiming benefit of this application, and particularly without prejudice to determination of equivalents of subject matter of this application or any later application claiming benefit of this application.

The pending claims are directed to methods of identifying a member of a mass-coded combinatorial library that is a ligand for a first biomolecule. The mass-coded combinatorial library is of the general formula XY_n, wherein n is an integer from about 2 to about 6, X is a scaffold and each Y is, independently, a peripheral moiety. Each peripheral moiety Y is derived from a member of a peripheral moiety subset, which is selected by choosing every set of two different peripheral moiety precursors from a peripheral moiety precursor set, the choosing being performed such that for each set of two, if the two peripheral moiety precursors have equal molecular masses, then one of the two is removed to form a remaining set. From the remaining set, every set of four peripheral moiety precursors is chosen, such that for a given set of four, one of the four peripheral moiety precursors is removed if a sum of the molecular masses of a first two precursors in the given set of four equals a sum of the molecular masses of a second two precursors in the given set of four peripheral moiety precursors, forming a remainder set. From the remainder set, every set of six different peripheral moiety precursors is chosen, including for a given set of six, removing one of the six peripheral moiety precursors if a sum of the molecular masses of a first three precursors in the given set of six equals a sum of the molecular masses of a second three precursors in the given set of six, forming a working selection set of peripheral moiety precursors. From the working selection set of peripheral moiety precursors, a peripheral moiety precursor subset is chosen such that the subset includes a sufficient number of peripheral

moiety precursors that there exist at least about 250 distinct combinations of n peripheral moieties derived from said subset, and wherein each of at least about 90% of the combinations of n peripheral moieties derived from said subset has a molecular mass sum that is distinct from the molecular mass sum of all other combinations of n peripheral moieties derived from said subset.

Claims 16, and 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Hsieh *et al.* (Molec. Diversity (1996) vol. 2, pp. 189-196) ("Hsieh") in view of Carrell *et al.* (Chemistry and Biology (1995) vol. 2 (3), pp. 171-183) ("Carrell"), or in the alternative as being unpatentable over Breeman *et al.* (Anal. Chem. (1997)) ("Breeman") in view of Carrell. It is asserted in the Action that Hsieh discloses identification of members of a small molecule library as ligands for target biomolecules by allowing complexes between the biomolecule and library members to form in solution, separating complexes from unbound library members by passing the mixtures over a size-exclusion chromatography column, dissociating the complexes, and identifying the ligands by mass spectrometry. (See the Action, p. 3, last paragraph.) As is conceded in the Action, Hsieh does not teach a mass-coded combinatorial library having the general formula XY_n, wherein n is 2-6 and there are at least 250 distinct combinations of n peripheral moieties, wherein at least about 90% of the combinations of n peripheral moieties have a distinct molecular mass as recited in the claims. (See paragraph bridging pages 3-4 of the Action.) As Hsieh does not teach a mass-coded library, it follows that neither does Hsieh teach or suggest methods for choosing members of such a library.

It is further asserted in the Action that Breeman teaches identification of members of a library which are ligands for an enzyme wherein the enzyme and library members are allowed to associate in solution in an ultrafiltration chamber, on one side of an ultrafiltration/size exclusion member unbound library members are washed away (through the membrane), whereas bound members are dissociated from the enzyme and identified by mass spectrometry. (See the Action, p. 5, paragraph 4.) As with Hsieh, it is conceded in the Action that Breeman does not teach a library comprising at least 250 members wherein at least 90% of the members have distinct molecular mass sums. (See the Action, p. 5, paragraph 4.) Because Breeman does not teach a mass-coded combinatorial library, it follows that Breeman does not teach or suggest methods for choosing members of such a library.

In the Action, Carrell is combined with Hsieh and Breeman respectively to provide the missing teaching of a mass-coded library. It is asserted in the Action that Carrell teaches synthesis of a peptide combinatorial library for use in screening wherein building blocks for the library are chosen such that "nearly all the compounds would possess a unique molecular weight." (See the Action p. 4, first full paragraph.) Although it is stated in the Action that Carrell does not teach a library of at least 250 compounds wherein at least 90% have a distinct molecular weight, it is asserted in the Action that Carrell teaches a library of over 50,000 different compounds, teaches a computer program to choose combinations of building blocks to provide a library wherein "nearly all" members have a unique molecular weight, and that the combination of teachings renders Applicants' claimed subject matter obvious. Applicants traverse.

The assertion in the Action that Carrell "teaches a library for screening which comprises over 50,000 different molecules" is an overbroad interpretation. Applicants submit that this statement cannot be construed as meaning that the library has 50,000 members, each with a unique mass. Read in context (p. 176 col. 1, where Carrell discusses the hypothetical situation where 75% of the expected Trp-containing compounds in a library are absent), that statement can only be taken to mean that each member may differ by structure, but does not necessarily possess unique mass relative to the other members of the library. For example, by evaluating the outcome of building block reactions with scaffold 2 (p. 172), any combination of four different building blocks results in a minimum of 6 different regioisomeric compounds with the same molecular weight. In fact, the only compounds in the library with a unique molecular weight are those having a scaffold with attachment of the same building block in all four positions. This means that of the 65,341 compounds theoretically present in Carrell's library based on scaffold 2 and reaction of 19 amino acid analogs, only 19 final compounds possess unique molecular weights. (See also p. 182, Table 3) As such, the quoted passage does not describe Applicants' claimed subject matter, a library where at least 90% of the compounds have a unique mass.

The assertion that Carrell teaches a computer program that chooses combinations of building blocks to provide a library where "nearly all" members have a unique mass is also an over interpretation of Carrell. Carrell provides no indication of what the program is, nor how the program "chooses" the building blocks. Applicants submit that because the quoted passages in

Carrell provide no indication of how one would select the building blocks nor an indication that the entire membership (or over 90%) of the library of compounds (as opposed to a subset of the library) would necessarily have a unique mass, Carrell does not teach or suggest Applicants' claimed subject matter, methods having the specifically delineated steps for making mass-coded libraries having the defined characteristics.

In no instance does Carrell teach a method for identifying a compound that is a ligand for a biomolecule where the compound is a member of a mass coded library, as recited in the presently pending claims. In fact, in screening the library against trypsin, Carrell actually teaches an alternate and much more cumbersome technique. Carrell specifically states (p. 172, Col. 1), "As our libraries were not made sequentially on a solid support, we were unable to make use of available bead-selection strategies or coding schemes." (i.e. including mass-encoding schemes) "Instead, an iterative selection procedure was designed through modification and generalization of a screening method first employed by Houghten and colleagues." Carrell then teaches and exemplifies with this trypsin screen (p. 176, Col. 2), a lengthy, complex process involving 7 rounds of sub-library synthesis and evaluation in order to identify active compounds. This is different and distinguishable from Applicants' claimed subject matter, wherein the entire unique-mass library is created and tested, and whereby iterative sub-library synthesis (as exemplified in Carrell) is not required. Thus, Carrell does not teach the use of mass-encoded mixtures as a means to identify compounds that are a ligand for a biomolecule as recited in the presently pending claims.

The presently pending claims have been amended to recite specific steps for choosing a peripheral moiety precursor subset such that at least about 90% of the combinations of n peripheral moieties, which are derived from the peripheral moiety precursor subset, have a distinct molecular mass. (See e.g., claim 1 (a)(i)-(a)(iv).) Carrell does not disclose a method of choosing a peripheral moiety precursor subset as recited in the presently pending claims (e.g., choosing every set of two different peripheral moiety precursors from a peripheral moiety precursor set, the choosing being performed such that for each set of two, if the two peripheral moiety precursors have equal molecular masses, then one of the two is removed to form a remaining set, etc.). Moreover, Carrell does not teach or suggest a mass-coded combinatorial library of the formula XY_n, wherein each Y is a peripheral moiety and is derived from a member

of a subset of n peripheral moiety precursors that is chosen as described in steps (a)(i)-(a)(iv), as required by the presently pending claims.

To establish a *prima facie* case of obviousness, three requirements must be met: (i) there must be some suggestion or motivation in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference; (ii) there must be a reasonable expectation of success; and (iii) the prior art reference(s) must teach or suggest all the claimed limitations. MPEP 2143. For reasons delineated below, Applicants submit that one or more of these requirements is not met, and a *prima facie* case of obviousness is not established.

As none of Hsieh, Breeman or Carrell disclose methods for choosing peripheral moiety precursors as recited in steps (a)(i)-(a)(iv) of claim 16, the combinations of both Hsieh with Carrell and Breeman with Carrell fail to teach or suggest each limitation of the pending claims as is required to establish a *prima facie* case of obviousness. That is, the combinations of references do not teach or suggest the steps and characteristics of the mass-coded combinatorial library that are specifically delineated in the pending claims. A *prima facie* case of obviousness has not been established as at least requirement (iii) above is not met. Thus Applicants submit that the combinations of Hsieh with Carrell and Breeman with Carrell do not render the presently pending claims obvious, and request that the corresponding rejections be withdrawn.

Claims 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hsieh in view of Carrell in further view of Rebek et al. (WO 95/19359) ("Rebek"). Claims 17 and 18 are dependent on claim 16, which recites a mass-coded combinatorial library comprising at least 250 combinations of moieties wherein at least 90% of the members of the library have a distinct molecular weight. It is asserted in the Action that Rebek teaches that members of a combinatorial library that bind to a protein may be identified using a protein that is immobilized on a solid support. (See the Action p. 6, second full paragraph.) Rebek does not teach a mass-coded library comprising at least 250 combinations of moieties wherein at least 90% of the members of the library have a distinct molecular weight as required by the presently pending claims (and is not relied upon for such a teaching). (See the Action, p. 6, second full paragraph.) Accordingly, the combination of Hsieh, Carrell and Rebek fail to teach each element of the claims as required to make a *prima facie* case of obvious, again, by failing to teach or suggest all of the steps and characteristics of the mass-coded library delineated in the claims. As such, a

prima facie case of obviousness is not established. In view of the foregoing, Applicants submit that the presently pending claims are unobvious and request that the rejection be withdrawn.

Similarly to claims 16-22, new claims 73-76 are directed to methods of identifying a member of a mass-coded combinatorial library that is a ligand for a first biomolecule. New claims 73-76 also recite steps to produce the mass-coded combinatorial library, including reciting steps of choosing a peripheral moiety precursor subset. Applicants submit that new claims 73-76 are novel and are also unobvious for at least the same reasons that claims 16-22 are unobvious. Accordingly, Applicants request new claims 73-76 be allowed.

Enclosed is a $930.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing attorney docket number 10845-014002.

Respectfully submitted,

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